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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/959,160	10/28/1997	ALBERT S. BALDWIN	5470-148	4280

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EXAMINER	
MCKELVEY, TERRY ALAN	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 11/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/959,160	BALDWIN ET AL.	
	Examiner	Art Unit	
	Terry A. McKelvey	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-8,14-16 and 29-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-8,14-16 and 29-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 1-3, 6-8, 14-16, and 29-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adams et al (U.S. Patent No. 5,780,454) in view of Gjerset (U.S. Patent No. 6,054,467). This rejection is maintained for reasons of record set forth in the Office Action mailed 5/20/03, and repeated below. Applicants' arguments filed 8/21/03 have been fully considered but they are not deemed to be persuasive.

Adams et al teach the administration of proteasome inhibitors for treating specific conditions in animals that are mediated or exacerbated, directly or indirectly, by proteasome function, such as cell proliferative diseases such as cancer (column 6). This reference specifically teaches reducing the activity of NF-kB in an animal (such as a mammal) comprising contacting the cells of the animal with a proteasome inhibitor (column 20), and reducing the rate of degradation of p53 protein in an animal (preferably, an animal subjected to DNA damaging drugs or radiation) comprising administering to said animal a

proteasome inhibitor (column 21). Adams et al teach that: "The use of proteasome inhibitors provides a method for augmenting the expression of p53 in normal cells by preventing its degradation by the proteasome. An example of this would be the systemic administration of proteasome inhibitor at a sufficient dose to inhibit p53 degradation by the proteasome during the treatment of the tumor with cytotoxic drugs or radiation. This will prolong and increase the levels of p53 expression in normal cells and will enhance the arrest of normal cell proliferation, reducing their sensitivity to higher doses of radiation or cytotoxic drugs. ... Thus, proteasome inhibitors can be used as adjuvants to therapy with tumericidal agents, such as radiation and cytotoxic drugs." (column 24). This reference also teaches that compounds of the present invention (proteasome inhibitors) inhibit the growth of cancer cells and that they can be administered to treat any cancer, including specific cancers (which encompass breast cancer) (columns 27-28).

Adams et al do not specifically teach administration of an anthracyclene antibiotic such as doxorubicin as the cytotoxic drug to be administered with a proteasome inhibitor.

Gjerset teaches a method for the induction of p53-mediated apoptosis in a cell comprising the step of contacting the cell with at least one inhibitory agent that inhibits DNA repair.

This method may further comprise contacting the cell with a first stimulatory agent that increases the level of a tumor suppressor in said cell, and that the tumor suppressor may be p53 (column 2). This reference also teaches that the method may also comprise the step of providing a DNA-damaging agent, that suitable DNA-damaging agents include daunorubicin and doxorubicin, and that tumor cells that are contemplated targets include breast tumor cell (columns 2-3). It is taught that delivery of the inhibitory agent, the stimulatory agent and/or the DNA damaging agent is advantageously via direct intratumoral injection, and in a more specific embodiment, the injection comprises continuous perfusion of the tumor (column 3) (which reads on simultaneous administration of the agents.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the cancer treatment method by proteasome inhibitor/cytotoxic drug administration taught by Adams et al by using as the cytotoxic drug doxorubicin as taught by Gjerset because Adams et al teach that it is within the ordinary skill in the art to administer a proteasome inhibitor (which augments p53 expression by preventing degradation of p53) with a cytotoxic drug to treat cancer, including cancers encompassing breast cancer, and Gjerset teaches that it is within the ordinary skill in the art

to treat cancer, such as breast cancer, by contacting animals with a composition comprising an inhibitory agent that inhibits DNA repair, and a first stimulatory agent that increases the level of p53 in said cell, and that the method may also comprise providing a DNA-damaging agent such as daunorubicin and doxorubicin in the composition.

One would have been motivated to do so for the expected benefit of using a known cancer-treating cytotoxic drug, doxorubicin, in the proteasome inhibitor/cytotoxic drug cancer treatment taught by Adams et al, which particular drug is known to be useful for treating cancer when coadministered with an agent that augments p53 expression as taught by Gjerset. Selection of a known material based upon its suitability for the intended use is obvious. Based upon the teachings of the cited the references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Regarding the different preambles of the claimed invention, such as "A method of enhancing the cytotoxic effects of an antineoplastic chemotherapeutic agent ...", "A method of enhancing chemotherapeutic cytotoxicity in a mammalian subject ...", "A method of treating a tumor in a mammalian subject ...",

"A method of treating a mammalian subject receiving a chemotherapeutic agent ...", and "A method of increasing the cytotoxicity of a chemotherapeutic agent ...", the preambles indicate the intended use of the claimed method which is defined by the method steps. Although the combination of the cited references may result in a method which does not have precisely the same intended use, the resulting method is the same because it comprises the same method steps (administering a proteasome inhibitor and doxorubicin to mammals suffering from cancer). Intended use limitations hold little patentable weight where the method steps can stand alone. Also, performing the method steps made obvious from the combined teachings of the recited references would inherently result in what is claimed in the preambles, such as increasing cytotoxicity of the chemotherapeutic agent.

Response to Arguments

The applicant argues that given that the underlying theory of Gjerset is treatment of subjects in which endogenous p53 is mutated to inactive form by replacement with exogenous p53, there is no reason one of ordinary skill in the art would be suggested to or motivated to administer such a patient a proteasome inhibitor suggested by Adams to reduce the rate of

degradation of endogenous p53, as Gjerset is concerned with the defectiveness of the endogenous p53 in the first place. It is further argued that nor could there be an expectation of success for such a combination, as Gjerset is replete with reference to the problem of mutated inactive endogenous p53, and that one skilled in the art would expect upregulation of endogenous p53 as taught by Adams to dilute out any beneficial effect of administering an exogenous p53 as taught by Gjerset.

The applicant's arguments are not persuasive for the following reasons. The applicant is essentially arguing a rejection that was not made: the rejection of the claims over Gjerset in view of Adams. The rejection of record is based upon the obviousness of the claims over Adams et al in view of Gjerset. The rejection did not suggest that it was obvious to administer to a patient of Gjerset, a proteasome inhibitor. There was no suggestion to reduce the rate of degradation of endogenous p53 in the method of Gjerset. The reasonable expectation of success was not for the combination of Gjerset in view of Adams, but instead for the combination of Adams et al in view of Gjerset. Therefore, the applicant's arguments drawn to a non-existent combination of cited references are not persuasive.

The basis of the rejection is that Adams et al teaches use of proteasome inhibitor in treating cancer (which operates by increasing the level of wild type p53, a tumor suppressor, in the cell), and that proteasome inhibitors can be used as adjuvants to therapy with tumericidal agents, such as radiation and cytotoxic drugs. Gjerset was cited to show that it would have been obvious to use an anthracyclene antibiotic such as doxorubicin as the cytotoxic drug to be administered with a proteasome inhibitor in the method of Adams et al, because Gjerset teaches use of a DNA-damaging agent such as daunorubicin and doxorubicin, in combination with an agent that increases the level of a tumor suppressor, such as p53, in a cancer cell, to treat cancer. Thus, this reference teaches one of skill in the art that daunorubicin and doxorubicin are specifically useful for cancer treatment in situations where p53 levels are increased, which reads on the method of Adams et al which also relies upon increasing p53 level, as part of the treatment with other cytotoxic drugs that are tumericidal agents. Thus, daunorubicin and doxorubicin are obvious cytotoxic agents to use in the method of Adams et al. Also, even in the absence of teachings concerning p53 levels, as shown by the reference, daunorubicin and doxorubicin are well known in the art as cytotoxic agents for treatment of cancer, and as such clearly

would have been obvious for use in the method of Adams et al which comprises use of a proteasome inhibitor in conjunction with tumericidal agents, such as cytotoxic drugs.

Finally, the applicant noted that the present invention is based upon a different mechanism than the mechanisms taught in either Adams or Gjerset, and an advantage of the instant invention is that it would work whether p53 is functional in the host subject or not. This argument is not persuasive because the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened

statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is 703-872-9306. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning rejections or other major issues in this communication or earlier communications from the examiner should be directed to Terry A. McKelvey whose telephone number is (703) 305-7213. The examiner can normally be reached on Monday through Friday, except for Wednesdays, from about 7:30 AM to about 6:00 PM. A phone message left at this number will be

responded to as soon as possible (i.e., shortly after the examiner returns to his office).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Terry A. McKelvey, Ph.D.
Primary Examiner
Art Unit 1636

November 16, 2003